UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,095	11/02/1998	BRIAN BURCHELL	MUR-7450	1739

7590 09/09/2003

Fish & Richardson P C
225 Franklin Street
Boston, MA 02110-2804

EXAMINER	
SHEINBERG, MONIKA B	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/142,095	BURCHELL, BRIAN	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Response to Amendment filed: 09 June 2003

The cancellation of claims 15-22 and the addition of new claims 23-25, is acknowledged.

Applicants' arguments, filed: 09 June 2003, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

- Claim 1 had been previously cancelled in the response filed: 28 January 2002.
- Claims 2-14 had been previously cancelled in the response filed: 11 September 2002.
- Claims 15-22 are cancelled.
- Claims 23-25 are new.
- Claims 23-25 are pending and hereby examined.

Claim Rejections - 35 USC § 103 – New

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

- Claims 23 and 24 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Bosma *et al.* (*N. Engl. J. Med.*, 1995) in view of Sibille *et al.* (*Eur. J. Clin. Pharmacol.*, 1990).
  - Bosma *et al.* teaches the genetic basis of the reduced expression of bilirubin UDP-glucoronosyltransferase 1 (UGT1) in Gilbert's Syndrome by the amplification of the specific regions of $(TA)_6TAA$ and $(TA)_7TAA$ for genotyping homozygous and heterozygous subjects of the TATAA element as recited in claims 23 for genotypes 6/6, 6/7 and 7/7. As required by claim

24, Bosma *et al.* demonstrates the collection of blood for sample analysis (p. 1172, line 6) from which DNA is isolated for the genetic analysis required in claim 23.

- Bosma *et al.* does not teach the use of such a genetic analysis for clinical drug trials that involves screening individuals for participation in a clinical drug trial. Sibille *et al.* teaches a laboratory screening method for the selection of healthy volunteers. Specifically, Sibille teaches:

> the aim of laboratory screening in phase I is to exclude subjects with subclinical illness, who might be at increased risk in the study, and who might also adversely influence interpretation of the results (Summary, p. 475).

In addition, the screening is carried out on the basis of abnormal levels of bilirubin, which found in patients with Gilbert's Syndrome (Table 3, p. 477).

It would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to perform the analysis of genetic basis for Gilbert's syndrome specific to the TATAA elements as taught by Bosma *et al.* and modify the method to be utilized for laboratory screening of individuals for clinical trials as per the teachings of Sibille *et al.* One of ordinary skill in the art would have been motivated to combine the teachings of Bosma *et al.* and Sibille *et al.* due to the advantages of excluding subjects from a drug trial whose illness, albeit benign or not, might result in adverse affects upon the subject and/or test results in a drug trial. Thus it would have been obvious to screen candidates for Gilbert's Syndrome, as this condition would have led to skewed and inaccurate results at best, and may have also been to the determent of the subject's health. Bosma *et al.* teaches a correlation between the genotype and phenotype as seen in the conclusion of the abstract in that the genotype is still required for Gilbert's Syndrome yet the "complete manifestation of the syndrome", phenotype, does not necessarily occur. Therefore a detection of the genotype although one may appear to be a healthy individual, would still determine a person as having Gilbert's Syndrome. Thus the individual maintains a "subclinical illness" status that one of ordinary skill in the art would be motivated to exclude from clinical trials as per Sibille *et al.* so as not to "adversely influence interpretation" of laboratory results (summary, 1st paragraph). Bosma *et al.* clearly states that although full manifestation of the syndrome may not occur alone, "[t]he present of other inherited or acquired factors affecting bilirubin metabolism, in addition to reduced glucuronidation, may result in the

full manifestation of the syndrome" (p. 1174, 1st column, last paragraph). Thus it would be obvious for one of ordinary skill in the art to expect potential adverse reactions or adverse interpretation of results to clinical trials for those of the specified genotypes, leading to the motivation to exclude them from participation in clinical trials requiring healthy candidates.

- Claim 25 is rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Bosma *et al.* (*N. Engl. J. Med.*, 1995) in view of Sibille *et al.* (*Eur. J. Clin. Pharmacol.*, 1990) as applied to claims 23 and 24 above; and further in view of Comings (US Patent 5,260,196; 9 November 1993).
  - The teachings of Bosma *et al.* in view of Sibille *et al.* are set forth as above.
  - Bosma *et al.* and Sibille *et al.* do not teach the buccal smear as the source of a biological sample (claim 25). Comings generally teaches that DNA can be obtained from buccal smears for genetic analysis (column 5, lines 54-56).

It would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to perform the analysis of genetic basis for Gilbert's syndrome specific to the TATAA elements as taught by Bosma *et al.* and further modify the biological sample collection to included buccal smears for isolating DNA as per the teachings of Comings. The DNA isolated from a blood sample of Bosma *et al* is functionally equivalent to DNA obtained from a buccal smear. It would be obvious for one of ordinary skill in the art at the time the invention was made to obtain a DNA by either blood collection or buccal smears to obtain DNA as required by the claimed invention absent evidence to the contrary. One of ordinary skill in the art would have been motivated to use buccal smears for sample collection for its simple and common means of quick genetic sample analysis that can be used in place of blood samples.

Response to Arguments

- The response filed: 09 June 2003, asserts that "Bosma *et al.* and Sibille *et al.*, no matter how combined, would not lead one skilled in the art to screen candidates for clinical trials in order to determine if they possessed the 6/6/, 6/, or 7/7 genotype" (please note the typographical errors are as written in the response) thus cannot render the instant invention obvious (p. 4, 1st

paragraph). In addition, applicants argue that Bosma *et al.* does not teach a "correlation between genotype and phenotype that would suggest usefulness of the genetic test as a criteria for clinical trials" (p.3, 1st paragraph). This is not found persuasive because Bosma *et al.* does teach a correlation between the genotype and phenotype as seen in the conclusion of the abstract in that the genotype is still required for Gilbert's Syndrome yet the "complete manifestation of the syndrome", phenotype, does not necessarily occur. Therefore a detection of the genotype although one may appear to be a healthy individual, would still determine a person as having Gilbert's Syndrome. Thus the individual maintains a "subclinical illness" status that one of ordinary skill in the art would be motivated to exclude from clinical trials as per Sibille *et al.* so as not to "adversely influence interpretation" of laboratory results (summary, 1st paragraph). Bosma *et al.* clearly states that although full manifestation of the syndrome may not occur alone, "[t]he present of other inherited or acquired factors affecting bilirubin metabolism, in addition to reduced glucuronidation, may result in the full manifestation of the syndrome" (p. 1174, 1st column, last paragraph). Thus it would be obvious for one of ordinary skill in the art to expect potential adverse reactions or adverse interpretation of results to clinical trials for those of the specified genotypes, leading to the motivation to exclude them from participation in clinical trials requiring healthy candidates.

Applicants also argue that Sibille *et al.* does not mention Gilbert's Syndrome. This is not found to be persuasive for reasons that Sibille *et al.* demonstrates the purpose of screening individuals prior to acceptance or decline from entering clinical trials based upon the individuals having subclinical illnesses. In addition, the screening is carried out on the basis of abnormal levels of bilirubin, which is found in patients with Gilbert's Syndrome (Table 3, p. 477), a phenotype detection means of the syndrome as seen in Bosma *et al.* As described above, it would be obvious for one of ordinary skill in the art to expect potential adverse reactions or adverse interpretation of results to clinical trials for those of the specified genotypes as demonstrated in Bosma *et al.*, leading to motivation to exclude them from healthy candidates for clinical trials as demonstrated in Sibille *et al.* Therefore, the arguments were non-persuasive to overcome the prior art.

Claim Objections

- Claim 23 is objected to because of the following informalities: step (e) has a typographical error in which "whether" is repeated twice. Appropriate correction is required.

Conclusion

- Claims 23 and 24 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Bosma *et al.* in view of Sibille *et al.*
- Claim 25 is rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Bosma *et al.* in view of Sibille *et al.* as applied to claims 23 and 24; and further in view of Comings.
- Claim 23 is objected to due to a typographical error.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal

Mail 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Souaya, can be reached at 703-308-6565. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

September 8, 2003
Monika B. Sheinberg
Art Unit 1634
MBS

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600